

Ahern, T. et al. (2016) Natural history, risk factors and clinical features of primary hypogonadism in ageing men: longitudinal data from the European Male Ageing Study. *Clinical Endocrinology*, 85(6), pp. 891-901.

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<http://eprints.gla.ac.uk/204139/>

Deposited on: 25 November 2019

Received Date : 10-Mar-2016
Revised Date : 29-May-2016
Accepted Date : 29-Jun-2016
Article type : 1 Original Article - UK, Europe

Natural History, Risk Factors and Clinical Features of Primary Hypogonadism in Ageing Men: Longitudinal Data from the European Male Ageing Study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cen.13152

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Short Title: Primary Hypogonadism in Ageing Men

Keywords: hypogonadism, andropause, testosterone, luteinizing hormone, ageing

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Acknowledgements:

The European Male Ageing Study is funded by the Commission of the European Communities Fifth Framework Program "Quality of Life and Management of Living Resources" Grant QLK6-CT-2001-00258 and facilitated by the Manchester Biomedical Research Centre and the NIHR Greater Manchester: Clinical Research Network. Additional support was also provided by Arthritis Research UK Centre for Epidemiology and the National Institute for Health Research and the Manchester Biomedical Research Centre. The Principal Investigator of EMAS is Professor Frederick Wu, MD; Andrology Research Unit, University of Manchester, Manchester, UK. The authors wish to thank the men who participated in the eight countries, the research/nursing staff in the eight centres: C Pott (Manchester), E Wouters (Leuven), M Nilsson (Malmö), M del Mar Fernandez (Santiago de Compostela), M Jedrzejowska, J Slowikowska-Hilczer, R Walczak-Jedrzejowska (Łódź), H-M Tabo (Tartu), A Heredi (Szeged) for their data collection, and C Moseley (Manchester) for

data entry and project co-ordination. Dr. D Vanderschueren is a senior clinical investigator supported by the Clinical Research Fund of the University Hospitals Leuven, Belgium.

Financial Disclosure: FCWW has acted as a consultant for Bayer-Schering, Eli Lilly and Besins Healthcare and also participated in advisory board meetings and lectured on their behalf. FCWW has received lecture fees from Bayer-Schering and Besins Healthcare. FCWW has received grant support (2010-2014) from Bayer Schering AG and Besins Healthcare. ITH is a consultant and/or has received grants from Ferring Pharmaceuticals, Takeda and Novartis. All other authors have nothing to disclose.

Funding: The European Male Ageing Study is funded by the Commission of the European Communities Fifth Framework Program “Quality of Life and Management of Living Resources” Grant QLK6-CT-2001-00258.

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Abstract

Objective: In ageing men, the incidence and clinical significance of testosterone (T) decline accompanied by elevated luteinising hormone (LH) are unclear. We describe the natural history, risk factors and clinical features associated with the development of biochemical primary hypogonadism (PHG, T<10.5nmol/L and LH>9.4U/L) in ageing men.

Design, Patients and Measurements: A prospective observational cohort survey of 3,369 community-dwelling men aged 40-79 years, followed up for 4.3 years. Men were classified as incident (i) PHG (eugonadal [EUG, T≥10.5nmol/L] at baseline, PHG at follow-up), persistent (p) PHG (PHG at baseline and follow-up), pEUG (EUG at baseline and follow-up)

and reversed (r) PHG (PHG at baseline, EUG at follow-up). Predictors and changes in clinical features associated with the development of PHG were analysed by regression models.

Results: Of 1,991 men comprising the analytical sample, 97.5% had pEUG, 1.1% iPHG, 1.1% pPHG, and 0.3% rPHG. The incidence of PHG was 0.2%/year. Higher age (>70 years) [OR 12.48 (1.27-122.13), $p=0.030$] and chronic illnesses [OR 4.24 (1.08-16.56); $p=0.038$] predicted iPHG. Upon transition from EUG to PHG, erectile function, physical vigour and haemoglobin worsened significantly. Men with pPHG had decreased morning erections, sexual thoughts and haemoglobin with increased insulin resistance.

Conclusions: Primary testicular failure in men is uncommon and predicted by old age and chronic illness. Some clinical features attributable to androgen deficiency, but not others, accompanied the T decline in men who developed biochemical PHG. Whether androgen replacement can improve sexual and/or physical function in elderly men with PHG merits further study.

Introduction

Low circulating testosterone (T) concentration is common in ageing men, increasing in prevalence from 20% to 50% between 60-80 years of age¹, but only a very small proportion develops symptomatic hypogonadism. In the European Male Ageing Study (EMAS) of 40-79 year-old community-dwelling men, the prevalence of low T (<10.5nmol/L) was 13.8%², but hypogonadism (defined by low T with 3 cognate symptoms) could be identified in only 2.1%³. Others have also found a significantly lower prevalence of symptomatic hypogonadism compared to that of biochemical hypogonadism (low T)⁴. Conspicuously, low T and putative hypogonadal symptoms are seldom detected in the same men, highlighting

their tenuous association and the substantial overlap between features of hypogonadism and those of ageing and chronic illness^{2,4}. Utilising changes in the tightly regulated feedback relationships in the hypothalamic-pituitary-testicular (HPT) axis, by combining gonadotrophin with T measurements, may enhance the precision of detecting, or predicting the advent, of unequivocal androgen deficiency in ageing men.

Biochemical hypogonadism can be divided into primary hypogonadism (PHG, elevated gonadotrophin level, testicular defect) and secondary hypogonadism (SHG, low or inappropriately normal gonadotrophin level, hypothalamic-pituitary defect)². Cross-sectional analyses of EMAS baseline data found PHG to be strongly associated with higher age, but not obesity, while SHG was predominantly found in connection with obesity, and was independent of age^{2,5}. In the present study, we report, for the first time, prospective observational data regarding the predisposing factors and clinical features of men who developed PHG.

Methods

Participants and study design

The study design (including the assessments described below in “*Other measures*”) and recruitment strategy for EMAS have been described previously^{6,7}. Briefly, an age-stratified sample of 3,369 men aged 40–79 (mean \pm SD: 60 \pm 11) years was recruited from population registers in eight European centres. Participants were assessed on two occasions separated by a median of 4.3 (range 3.0–5.7) years. Ethical approval for the study was obtained in accordance with local requirements in each centre. All participants provided written informed

consent. For this analysis, participants with disease of the pituitary, testes or adrenal glands and participants on medications known to affect androgen levels were excluded.

Hormone measurements

A single fasting morning (before 1000) blood sample was obtained at baseline and follow-up.

T was measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS)⁸, with paired baseline and follow-up samples analysed simultaneously. LH, FSH and SHBG were measured by the E170 platform electrochemiluminescence immunoassay (Roche Diagnostics). The Vermeulen formula was used to calculate free (f) T⁹. Intra- and inter-assay coefficients of variation (CV) were: T 4.0 and 5.6%; LH 1.9 and 2.7%; FSH 0.9% and 1.9%; and SHBG 1.9 and 3.2%. Insulin was assayed using chemiluminescence (CVs: 3.9% and 5%). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR)¹⁰.

Biochemistry/haematology

Standardised measurements were undertaken in laboratories in each centre.

Other measures

Participants answered questions about: smoking, alcohol consumption frequency and specific illness. A participant was considered to have a chronic illness if he had one (or more) of the following self-reported illnesses: heart problems, stroke, hypertension, diabetes, bronchitis, cancer, kidney disease or liver disease. Participants also completed quality of life questionnaires, which included ratings of general health (MOS 36-item Short-Form health survey [SF-36]), depression [Beck's Depression Inventory (BDI)], physical activity [Physical Activity Scale for the Elderly (PASE)] and sexual symptoms (EMAS Sexual Function

Questionnaire). As described previously, participants were dichotomised to symptomatic or asymptomatic according to pre-specified responses associated with differences in T levels³.

Body weight and height were measured by electronic scale and stadiometer (SECA UK).

Physical function was assessed by Reuben's Physical Performance Test (PPT) and cognitive processing speed by Wechsler's Digit-Symbol Substitution test (DSST).

Gonadal status

Participants were assigned gonadal status according to total T and LH levels. Current guidelines recommend use of total T rather than free T to define hypogonadism^{11,12}. Men with a $T \geq 10.5$ nmol/L were considered eugonadal (EUG) and men with a $T < 10.5$ nmol/L and a $LH > 9.4$ U/L were considered to have primary hypogonadism (PHG)². Subjects were categorised further by their *change* in gonadal status into one of four groups: (1) *persistent (p) EUG* – EUG at baseline and at follow-up; (2) *incident (i) PHG* - EUG at baseline and PHG at follow-up; (3) *persistent pPHG* - PHG at both baseline and follow-up; and (4) *reversed (r) PHG* - reversal of PHG at baseline to EUG at follow-up.

Statistical analysis

Baseline and follow-up characteristics were compared between groups using Mann-Whitney U or Kruskal-Wallis analyses for continuous variables and Chi squared tests for categorical variables. Post-hoc analyses were performed using Tukey-Kramer tests with correction for multiple pairwise comparisons. Multiple regression models were used to assess associations of clinical variables with iPHG, or pPHG, using pEUG as the referent group. In assessing potential risk factors for PHG, centre was included in the regression model as a random-effects variable and the potential risk factors as fixed-effects variables². Multiple regression

models were used also to adjust for baseline age (40-49 years, 50-59 years, 60-69 years, ≥ 70 years) and chronic illness (0, 1, ≥ 2 illnesses).

Results from linear regression models are presented as regression coefficients (for standardised variables) with 95% confidence intervals (CI) and from logistic regression models as odds ratios (OR) with CI. All statistical analyses were conducted using STATA version 13 (StataCorp, College Station, TX).

Results

Gonadal status transition

Of the 3,369 men that participated in EMAS, 1,991 men made up the main analytical sample after exclusion of those with known pituitary, testicular or adrenal disease (n=94), failure to attend for follow-up assessment (n=575), missing T or LH data (n=122), and SHG (n=369, Figure 1). Those currently using steroid hormones (n=11 at baseline, n=17 at follow-up), gonadotrophin-releasing hormone analogues (n=9 at baseline, n=3 at follow-up), anti-androgens (n=45 at baseline, n=31 at follow-up), 5-alpha reductase inhibitors (n=38 at baseline, n=46 at follow-up) and strong opioids (n=13 at baseline, n=4 at follow-up) were excluded also. Compared to the main analytical sample, men lost to follow-up (n=407) were older, had higher BMI, higher smoking prevalence, higher HOMA-IR, worse physical and cognitive function and had more illnesses (Supplemental Table 1). This was the case also for men who died (n=168) with the exception of no difference, compared to the main analytical sample, in BMI or HOMA-IR.

Amongst the 1,991 men in the analytical sample, 1,942 (97.5%) had pEUG and 22 (1.1%) developed PHG giving an annual incidence (95% confidence interval) of 0.24%/year (0.10-0.58) assuming linearity of PHG development. The prevalence of PHG at follow-up was 2.1% (n=49). Taking into account the baseline prevalence of PHG of 1.7% (n=54), the cumulative prevalence rate of PHG was therefore 3.1% amongst the EMAS cohort.

Of 54 men who had PHG at baseline, 18 (33.3%) were lost to follow-up, had medical exclusions or no follow-up hormone data. Of the remainder, 7 died (19.4%). Of the remaining men with PHG at baseline who had follow-up data (n=29), 22 (75.9%) continued to have PHG at follow-up, 5 (17.2%) reverted to EUG at follow-up and 2 (6.9%) developed SHG.

Cohort Characteristics

At baseline, age was higher, triglyceride to HDL-cholesterol ratio was higher and SF36 physical function score was lower in iPHG compared with pEUG men (Table 1). In addition, iPHG men had lower cognitive function (DSST). At follow-up, the differences in age, SF36 physical function score and DSST between the groups persisted, while iPHG men also had lower haemoglobin, a lower mean physical function rating (PPT, an objective measure of physical function). The prevalence of 2 or more illnesses and cardiovascular disease in the iPHG group was greater than that in the pEUG group at baseline and at follow-up. Erectile dysfunction was more prevalent in the iPHG group than in pEUG at follow-up, as was walking limitation and decreased vigour. Men with pPHG differed significantly from those with pEUG in the same parameters (as iPHG) except for the triglyceride to HDL-cholesterol ratio at baseline. In addition, men with pPHG had higher BMI and HOMA-IR and lower physical activity (PASE) and baseline haemoglobin compared to men with pEUG. Like men

with iPHG, those with pPHG had more illnesses and more sexual and physical symptoms than pEUG men.

Hormone levels

Baseline total T in iPHG (13.2 ± 2.3 nmol/L) was significantly lower than in pEUG (18.4 ± 5.4 nmol/L, $p < 0.05$, Figure 2). Total T decreased during follow-up to 9.3 ± 0.9 nmol/L in iPHG men and to 18.1 ± 5.4 nmol/L in pEUG men with a greater decline evident for iPHG men (mean changes -3.9 ± 2.7 nmol/L and -0.3 ± 4.1 nmol/L, $p < 0.05$). Total T decreased also in pPHG men (from 7.3 ± 2.4 nmol/L to 5.9 ± 2.9 nmol/L) and, by definition, rose in rPHG men (from 9.3 ± 1.4 nmol/L to 12.7 ± 1.2 nmol/L). Free T was already low in iPHG men (203 ± 55 pmol/L) at baseline and fell by 56 ± 23 pmol/L at follow-up. In pEUG men free T was 322 ± 80 pmol/L at baseline and fell by only 15 ± 70 pmol/L at follow-up. LH in the iPHG men was already elevated at baseline (16.5 ± 14.0 U/L) but did not increase further at follow-up (18.5 ± 11.5 U/L, $p > 0.05$) despite the substantial falls in total and free T. Mean LH level in pPHG men was elevated (20.2 ± 8.7 U/L) at baseline and remained unchanged at follow-up (22.1 ± 11.7 U/L $p > 0.05$). Similarly, mean LH level in rPHG men was 11.0 ± 1.6 U/L at baseline and remained elevated at follow-up (14.1 ± 5.6 U/L $p > 0.05$, $n=5$). FSH levels closely followed those of LH (results not shown). Mean SHBG levels were similar across all 3 groups at baseline and follow-up and increased slightly in the pEUG, pPHG and rPHG groups.

Risk factors

In a multiple logistic regression model, the oldest men [>70 years, OR 12.48 (1.27-122.13), $p=0.030$] and those with 2 or more illnesses [OR 4.24 (1.08-16.56), $p=0.038$] were significantly more likely to develop PHG during follow-up (Figure 3, iPHG vs pEUG).

Symptoms and functional ratings associated with PHG

At baseline, men who developed PHG during follow-up (iPHG) had lower sexual thought frequency, increased erectile dysfunction, decreased vigour (Figure 4A), lower haemoglobin, lower physical function, higher depression score and lower cognitive function than men who remained eugonadal (pEUG, Figure 4B). However, only erectile dysfunction and haemoglobin changed (worsened) more during follow-up in iPHG men than in pEUG men.

At follow-up, the prevalences of erectile dysfunction and decreased vigour were greater in the iPHG group than in the pEUG group. At follow-up also, men with iPHG had lower haemoglobin, lower physical function, higher depression score and lower cognitive function than men with pEUG.

After adjustment for age and chronic illness, the only parameters that remained significantly associated with iPHG (Figure 4, open symbols) were SF36 physical function score at baseline, fall in haemoglobin during follow-up and erectile dysfunction, decreased vigour and lower haemoglobin at follow-up. However, the power of these adjusted comparisons is limited by the small number of iPHG men due to the low incidence.

Among pPHG men (PHG at baseline and at follow-up), all three sexual symptoms were more prevalent at baseline and follow-up in comparison to pEUG men (Figure 5A). Frequency of sexual thoughts decreased and erectile dysfunction worsened more in the pPHG. Decreased vigour was more prevalent, at baseline and follow-up. Low mood was more prevalent in pPHG than in pEUG men at baseline only. Haemoglobin levels were significantly lower, and HOMA-IR values significantly higher, in pPHG at baseline and follow-up than in pEUG

(Figure 5B). SF-36 Physical Function score, PPT rating and DSST were similarly reduced at baseline and follow-up in pPHG, but only PPT rating worsened more.

After adjustment for age and chronic illness, decreased morning erections, haemoglobin and increased HOMA-IR at baseline and decreased sexual thoughts, haemoglobin and HOMA-IR at follow-up remained significantly associated with pPHG (Figure 5, open symbols). Again, the power of these adjusted comparisons is limited by the small number of pPHG men.

Discussion

We describe the natural history of, the predisposing factors for and the clinical features associated with biochemically-defined primary hypogonadism in the general population. Age-related biochemical PHG is a relatively uncommon entity predominantly affecting men over the age of 70 years with multiple illnesses who bear little resemblance to the burgeoning population of patients actively seeking testosterone replacement ¹³.

Natural history of PHG

The relative rarity of biochemical PHG in the EMAS population was indicated by a baseline prevalence of 1.7% and confirmed at follow-up by a prevalence 2.1%, giving an incidence of only 0.2%/year. In contrast, SHG is much more common having a baseline prevalence of 11.5%, and an 8-fold higher incidence of 1.6%/y^{2,14}. These figures cannot be directly compared with previously reported incidence of symptomatic hypogonadism of 10% over 9 years¹⁵ and prevalence estimates of >20% for overall hypogonadism in the ageing male population^{1,4,16}, since these earlier studies did not make the differentiation between PHG and SHG. These prevalence rates were determined after exclusion of men with disease of the

pituitary, testis or adrenal glands and of men on medications known to affect androgen levels
– the real-life prevalence rates are likely to be higher.

Ageing-related PHG appears to be mostly irreversible; T levels returned to normal in only 4.3%/year. This contrasts with SHG which, in EMAS, had a rate of reversal of 9.7%/year¹⁴. Of the original 54 men with PHG at baseline, 7 (13.0%) died during the follow-up period, which is 2.5-fold higher than in the whole study population. Hence, the state of PHG may beckon a serious deterioration in health. This is compatible with our, and others', previous finding that late-onset hypogonadism is associated with substantially increased mortality^{17,18}.

Risk factors for PHG

Advanced age and multiple chronic illnesses are the factors that most strongly predicted the development of iPHG. In this respect PHG differs substantially from the more common SHG – obesity predicted SHG, but age and chronic illness did not¹⁴. These important and consistent differences in the risk factors and natural history between PHG and SHG offer useful insights and guidance for clinical decision making in symptomatic older men presenting with low T.

There is a large body of evidence showing that T levels decrease with ageing in men, ranging in various longitudinal studies from 0.04 to 2.6% per year after the age of 40^{1,16,19-21}.

However, obesity strongly influences the magnitude of decline in T independent of age²¹.

There are also data suggesting that T levels can be maintained in highly selected elderly men who remain in good health²², making the case that it is not age *per se*, but ageing-related health deterioration that affects T production. The HPT axis is tightly regulated in men⁵ and LH levels are highly responsive to any deficits in Leydig cell function²³. Impaired testicular

response to LH can be caused by exposure to pro-inflammatory cytokines²⁴⁻²⁶, arising from chronic low grade inflammation²⁷, associated with ageing and chronic illness²⁶. It is well known that chronic illnesses associated with inflammation, such as cancer and obesity, are associated with multi-level disruption of the HPT axis²⁸. Many younger men with chronic illness have, therefore, low T with non-elevated LH level (SHG) due to such multi-level disruption. Our finding that chronic illness is a risk factor for PHG, but not SHG¹⁴ is consistent with recent data showing an independent association between elevated LH with cardiovascular disease²⁹ and decreased muscle strength³⁰. One can surmise, therefore, that excessive elevation of LH (over and above that associated with ageing per se and independent of T) can be regarded as a barometer of poor health in ageing men³¹.

Endocrinology of PHG

PHG is characterised by elevation of gonadotrophins that is unable to counteract impaired Leydig cell function. Only a relatively small proportion of elderly men develop PHG (vide supra) since the increased LH can mobilise sufficient testicular functional reserve to maintain T in the normal range in the vast majority, as demonstrated by the large number of men with compensated hypogonadism (i.e. normal T and elevated LH)². In the present prospective study, baseline mean LH (16.5 ± 14.0 U/L) was already significantly elevated in the iPHG men, which is compatible with a protracted compensated state and the successful deferment of testicular failure. During follow-up, total T declined significantly (from 13.2 ± 2.3 to 8.9 ± 2.1 nmol/L) in the iPHG group but LH showed little concurrent change (from 16.5 ± 14.0 to 18.5 ± 11.5 U/L). This suggests that the HPT axis had reached the limit of its compensating capacity possibly due to a superimposing element of hypothalamic dysfunction²³, thereby allowing testicular failure to supervene. Development of PHG can therefore be predicted

several years before gonadotrophic compensation reaches its limit and T eventually falls into the hypogonadal range.

Clinical characteristics of PHG

The development of biochemical PHG was associated with the development (or worsening) of erectile dysfunction, decreased vigour and lower haemoglobin. Many of the observed differences (from pEUG) in clinical characteristics were already apparent at baseline in those EUG men destined to develop PHG during follow-up. Although only a selection of these features remained statistically significant after adjustment for age and health status, there appears to be a trend of increasing symptoms and functional deficits across iPHG to pPHG (Figures 4 and 5). This trend is concurrent with the progressive decline in T and the duration of hypogonadism, although our observational data cannot ascribe causality to these associations. Interestingly, these findings tally well with those of the recently published Testosterone Trials where transdermal testosterone in older men (≥ 65 years) with a low T (≤ 9.5 nmol/L) had a small to medium positive effect on sexual function and small effect on physical function and mood³².

There are a number of potential explanations for the relatively limited number of statistically significant associations between the development of biochemical PHG with putative ‘hypogonadal’ features and functional deficits. The PHG group comprised older men (mean age over 65) in whom deteriorating health from chronic diseases gives rise to a multitude of symptoms and functional deficits, which overlap with those of androgen deficiency. The picture of presumed androgen deficiency in men developing PHG is therefore confounded by a background of non-specific features of senescence. The small number of men with iPHG and pPHG does not provide adequate statistical power to detect small differences (signals)

against the significant prevalence of background (noise) symptoms and deficits (unrelated to T levels). In iPHG men, LH was already higher, and their T significantly lower, at baseline, than in pEUG men. It can therefore be argued that the iPHG men were already borderline 'hypogonadal', i.e. they had compensated hypogonadism with relatively lower mean total T and in particular free T. This may have introduced biases against differentiating the characteristics of iPHG from pEUG. Notwithstanding these issues, the finding of associations between iPHG and pPHG with sexual symptoms, decreased vigour, physical function and haemoglobin suggest that biochemical PHG may identify a small group of men with clinical features compatible androgen deficiency.

Strengths and weaknesses

Strengths of EMAS include the number of participants, the simultaneous measurement of T by LC-MS/MS in paired baseline and follow-up samples and the breadth of the phenotypic data collected by the standardised instruments across centres and between the phases of the study. This provided an unprecedented opportunity to describe the natural history and the temporal sequences of the earliest clinical changes associated with the onset of biochemical hypogonadism in an unselected cohort of men from the general population. To date, no prospective studies have described the clinical features associated with the development of PHG.

The main limitation in this analysis is the relatively small number of men developing PHG during follow-up - this is unavoidable given the relative rarity of the condition which has not been previously described. This may have restricted the power of our analyses to clearly differentiate changes that could have been related to androgen deficiency from those due to age-related health deterioration. Even with the small number of cases, however, some

clinically useful insight has been captured. Other limitations in EMAS have been described previously^{6,7}. The mortality-adjusted retention rate of 86.2% may have introduced an unmeasured survivor bias, but this potential censoring of men with lower T or higher LH would have improved the validity of our internal comparisons. The relatively high attrition rate in the pPHG group may have mitigated against capturing a more consistent picture of the progression of clinical features of hypogonadism from iPHG. The follow-up period of 4.3 years is a relatively short time in which to capture the more subtle or gradual changes in signs and symptoms of androgen deficiency. At both study phases, only a single blood sample was available for determination of hormone levels. Multiple blood sample collection is impractical in large epidemiological surveys^{1,15} such as ours. Several studies have confirmed that T levels within the same individual do not fluctuate significantly when measured serially over several months³³⁻³⁶. It is therefore unlikely that single hormone determination in the present study would have introduced substantial misclassification of gonadal status. The fact that the vast majority of EMAS participants remained eugonadal attests to this. The consistency of higher LH between baseline and follow-up and the parallel changes in FSH also adds to the validity of the present results.

In conclusion, we have shown that only a small proportion (0.2%/year) of older men develops biochemical primary testicular failure, with the main risk factors being age >70 years and chronic illnesses. Concurrently, these men experienced worsening sexual and physical impairments with a fall in haemoglobin. However, not all clinical features suggestive of androgen deficiency could be unequivocally attributed to the development of primary hypogonadism due to various confounding factors associated with ageing. The present findings support further research, including the conduct of additional RCTs of sufficient size

and duration, to rigorously investigate both benefits and risks of hormone replacement in well-defined groups of older symptomatic men with low T.

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Figure Legends:

Figure 1: Flowchart of Participants

pEUG, persistent EUGonadism; pPHG, persistent Primary HypoGonadism; iPHG, incident Primary HypoGonadism; rPHG, reversed Primary HypoGonadism

*Men with secondary hypogonadism have been described previously – see Rastrelli, G. et al (2015). *J Clin Endocrinol Metab* **100**, 3172-3182

Figure 2: Testosterone, LH and SHBG Levels in relation to Gonadal Status at Baseline and Follow-up

Baseline and follow-up hormone concentrations are expressed as means and as standard errors of the mean (SEM). Data in the groups were compared, and p values were generated, using Kruskal-Wallis analyses and Tukey-Kramer post-hoc analyses to permit correction for multiple pairwise comparisons.

*, $p < 0.05$; ^a, follow-up hormone levels in this group differed significantly from the baseline hormone levels in the same group when analysed using the Wilcoxon Signed Ranks Test. pEUG, persistent EUGonadism; iPHG, incident Primary HypoGonadism; rPHG, recovery from Primary HypoGonadism.

The horizontal dotted lines represent the thresholds above or below which values are considered abnormal.

Figure 3: Potential Risk Factors for Primary Hypogonadism

Data are expressed as odds ratio (symbol) \pm 95% confidence interval (error bars). Odds ratios and p values were determined in the left panel using single independent variables (unadjusted) binary logistic regression analyses. Odds ratios and p values were determined in the right panel using multiple binary logistic regression analyses including all the potential risk factors listed in the same model.

*, $p < 0.05$; **, $p < 0.01$.

Figure 4: Relationships between Incident Primary Hypogonadism with Symptoms and Functional Ratings

Categorical data are expressed as odds ratios (symbol) \pm 95% confidence intervals (error bars). Continuous data are expressed as standardized regression coefficients (symbol) \pm 95%

confidence intervals (error bars). Regression coefficients, odds ratios and p values were determined using regression analyses comparing incident PHG to the referent group of persistent eugonadism.

The statistical analysis was first carried out without adjustment (▲) and then with adjustment for baseline age and chronic illness using multiple regression analyses (○).

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

- A) The odds ratios for the prevalence of symptoms at baseline are shown in the left panel and for the prevalence at follow-up are shown in the right panel. The middle panel shows the odds ratios for the incidence or worsening of symptoms.
- B) The standardized regression coefficients for baseline functional rating values are shown in the left panel, for follow-up values in the right panel and for the percentage change in values in the middle panel.

Figure 5: Relationships between Persistent Primary Hypogonadism with Symptoms and Functional Ratings

Categorical data are expressed as odds ratios (symbol) \pm 95% confidence intervals (error bars). Continuous data are expressed as standardized regression coefficients (symbol) \pm 95% confidence intervals (error bars). Regression coefficients, odds ratios and p values were determined using regression analyses comparing incident PHG to the referent group of persistent eugonadism.

The statistical analysis was first carried out without adjustment (▲) and then with adjustment for baseline age and chronic illness using multiple regression analyses (○).

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

A) The odds ratios for the prevalence of symptoms at baseline are shown in the left panel and for the prevalence at follow-up are shown in the right panel. The middle panel shows the odds ratios for the incidence or worsening of symptoms.

B) The standardized regression coefficients for baseline functional rating values are shown in the left panel, for follow-up values in the right panel and for the percentage change in values in the middle panel.

Table 1. Comparison of Baseline and Follow-Up Characteristics in Men with Incident and Persistent Primary Hypogonadism and those with Persistent Eugonadism

Parameter	Baseline				Follow-Up			
	pEUG	iPHG	pPHG	P ¹	pEUG	iPHG	pPHG	P ²
N	1,942	22	22		1,942	22	22	
Age, years	58.3 ±10.5	66.9 ±11.1 ^a	71.0 ±8.8 ^a	<.001	62.7 ±10.4 ⁱ	71.4 ±11.0 ^{ai}	75.4 ±8.7 ^{ai}	<.001
BMI, kg/m ²	27.1 ±3.8	28.1 ±3.1	30.1 ±4.2 ^a	<.001	27.2 ±3.9 ⁱ	28.1 ±3.6	29.6 ±5.0 ^a	0.043
Smoking, n (%)	398 (20.7)	7 (31.8)	2 (9.5)	0.196	344 (18.3) ⁱ	6 (28.6)	2 (9.5)	0.278
Frequent Alcohol, n (%)	481 (24.9)	5 (22.7)	5 (22.7)	0.948	596 (35.2) ⁱ	9 (45.0) ⁱ	5 (27.8)	0.529
Pre-degree Education, n (%)	1,336 (70.3)	13 (61.9)	18 (81.8)	0.349	---	---	---	---
Living with Partner, n (%)	1,537 (84.8)	14 (77.8)	16 (84.2)	0.713	---	---	---	---
Trig/HDL	1.1 ±1.2	1.3 ±1.0 ^a	1.9 ±2.4	0.011	1.2 ±2.3	1.1 ±0.8	2.6 ±4.4 ^a	0.018
HOMA-IR	2.8 ±3.6	3.3 ±3.1	7.0 ±7.8 ^{ab}	<.001	2.8 ±3.0	3.0 ±1.6	7.0 ±8.4 ^{ab}	<.001
Hb, g/L	150 ±11	146 ±9	141 ±13 ^a	0.001	150 ±11	139 ±13 ^a	139 ±14 ^a	<.001

PASE score	207 ±88	181 ±108	142 ±92 ^a	0.004	183 ±94 ⁱ	164 ±112	127 ±82 ^a	0.016
PPT rating	24.3 ±2.4	23.2 ±2.8	23.1 ±2.1	0.010	23.8 ±2.5 ⁱ	22.0 ±2.7 ^{ai}	21.5 ±2.4 ^{ai}	<.001
SF-36 physical function	51.1 ±7.5	44.7 ±9.7 ^a	46.1 ±9.1 ^a	<.001	50.5 ±8.2 ⁱ	44.8 ±9.5 ^a	42.5 ±11.3 ^a	<.001
BDI	6.4 ±6.0	9.4 ±6.6	5.8 ±5.5	0.034	6.2 ±6.4	9.5 ±6.4	5.1 ±4.4	0.023
DSST	28.9 ±8.4	22.9 ±9.3 ^a	21.9 ±9.1 ^a	<.001	27.9 ±8.9 ⁱ	22.4 ±9.9 ^a	19.0 ±7.9 ^a	<.001
≥1 illness, n (%)	739 (38.1)	15 (68.2) ^a	19 (86.4) ^a	<.001	1,030 (53.0) ⁱ	17 (77.3)	19 (86.4) ^a	0.001
≥2 illnesses, n (%)	287 (19.3)	9 (56.3) ^a	7 (70.0) ^a	<.001	561 (38.1) ⁱ	14 (73.7) ^a	12 (80.0) ^a	<.001
Diabetes, n (%)	107 (5.6)	3 (13.6)	3 (14.3)	<i>0.067</i>	127 (6.7) ⁱ	4 (19.1)	4 (19.1)	0.008
CVD, n (%)	576 (30.1)	13 (59.1) ^a	15 (71.4) ^a	<.001	740 (40.6) ⁱ	14 (70.0) ^a	13 (68.4) ^a	0.002
Decreased morning erections, n (%)	623 (32.9)	10 (52.6)	15 (75.0) ^a	<.001	616 (34.4) ⁱ	8 (53.3)	13 (72.2) ^a	0.001
Decreased sexual thoughts, n (%)	430 (22.7)	9 (45.0)	12 (60.0) ^a	<.001	480 (26.6) ⁱ	8 (47.1)	14 (73.7) ^a	<.001
Erectile dysfunction, n (%)	466 (24.8)	9 (45.0)	13 (65.0) ^a	<.001	537 (31.0) ⁱ	11 (73.3) ^a	13 (76.5) ^a	<.001
Limited walking >1km, n (%)	31 (1.6)	0 (0.0)	5 (22.7) ^a	<.001	73 (3.9) ⁱ	3 (15.8) ^a	5 (22.7) ^a	<.001
Decreased vigorous activity, n (%)	371 (19.3)	8 (40.0)	9 (40.9) ^a	0.003	448 (24.0) ⁱ	12 (60.0) ^a	12 (54.6) ^a	<.001

Unable to bend, n (%)	82 (4.3)	5 (25.0) ^a	4 (18.2) ^a	<.001	94 (5.0)	2 (10.0)	1 (4.6)	0.599
Fatigue, n (%)	73 (3.8)	2 (10.0)	1 (4.6)	0.351	81 (4.3)	1 (5.0)	1 (4.8)	0.984
Low mood, n (%)	71 (3.7)	2 (10.5)	3 (14.3) ^a	0.014	72 (3.9)	1 (5.0)	2 (9.5)	0.412
Loss of energy, n (%)	76 (3.9)	2 (10.5)	0 (0.0)	0.216	106 (5.6) ⁱ	2 (10.0)	2 (9.1)	0.560

Data are expressed as mean \pm standard deviation for continuous variables or as number (percentage) for binary categorical variables.

Abbreviations: pEUG, $T \geq 10.5$ nmol/L at both baseline and follow-up; iPHG, $T \geq 10.5$ nmol/L at baseline, $T < 10.5$ nmol/L at follow-up and $LH > 9.4$ U/L at follow-up; pPHG, $T < 10.5$ nmol/L and $LH > 9.4$ U/L at both baseline and follow-up; BMI, Body Mass Index; HOMA-IR, HOmeostatic Model of Insulin Resistance; Hb, haemoglobin SF-36, PASE, Physical Activity Scale for the Elderly; PPT, Physical Performance Test; Short-Form 36 questionnaire; DSST, Digital Symbol Substitution Test; BDI, Beck Depression Inventory; MetS, Metabolic Syndrome; CVD, CardioVascular Disease.

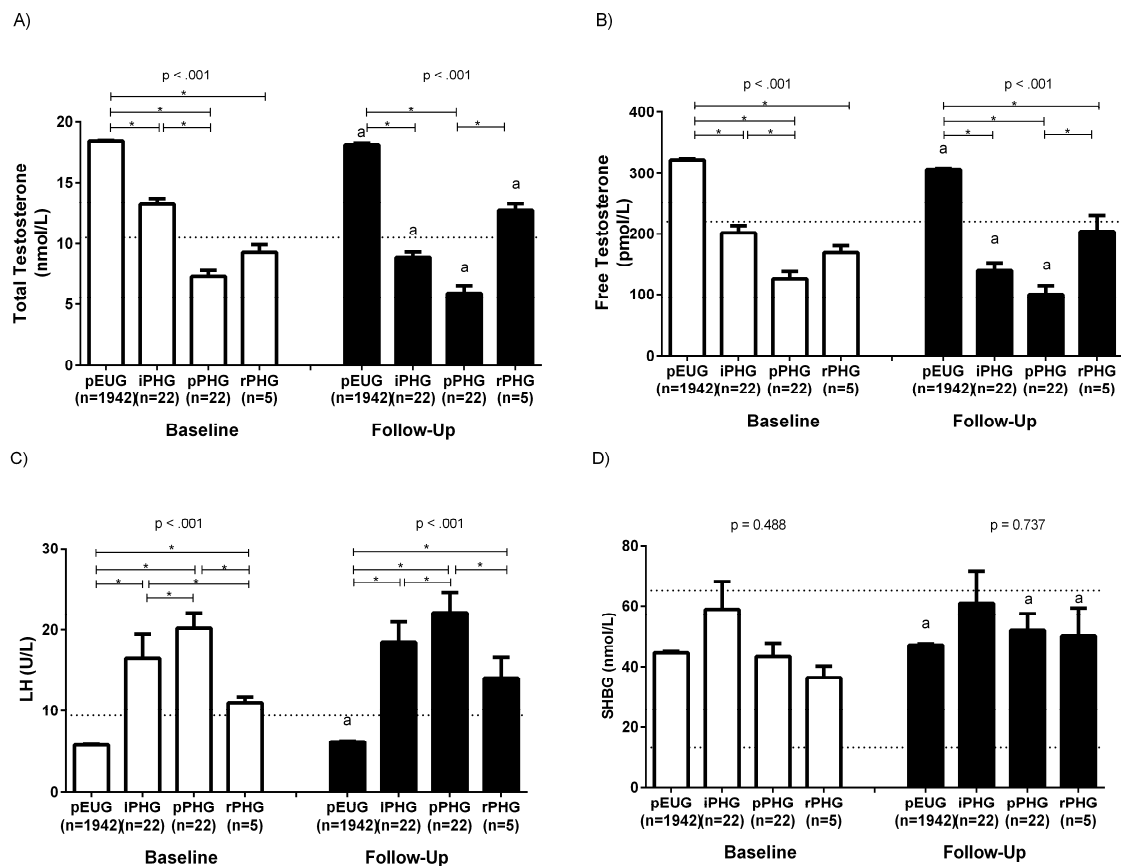
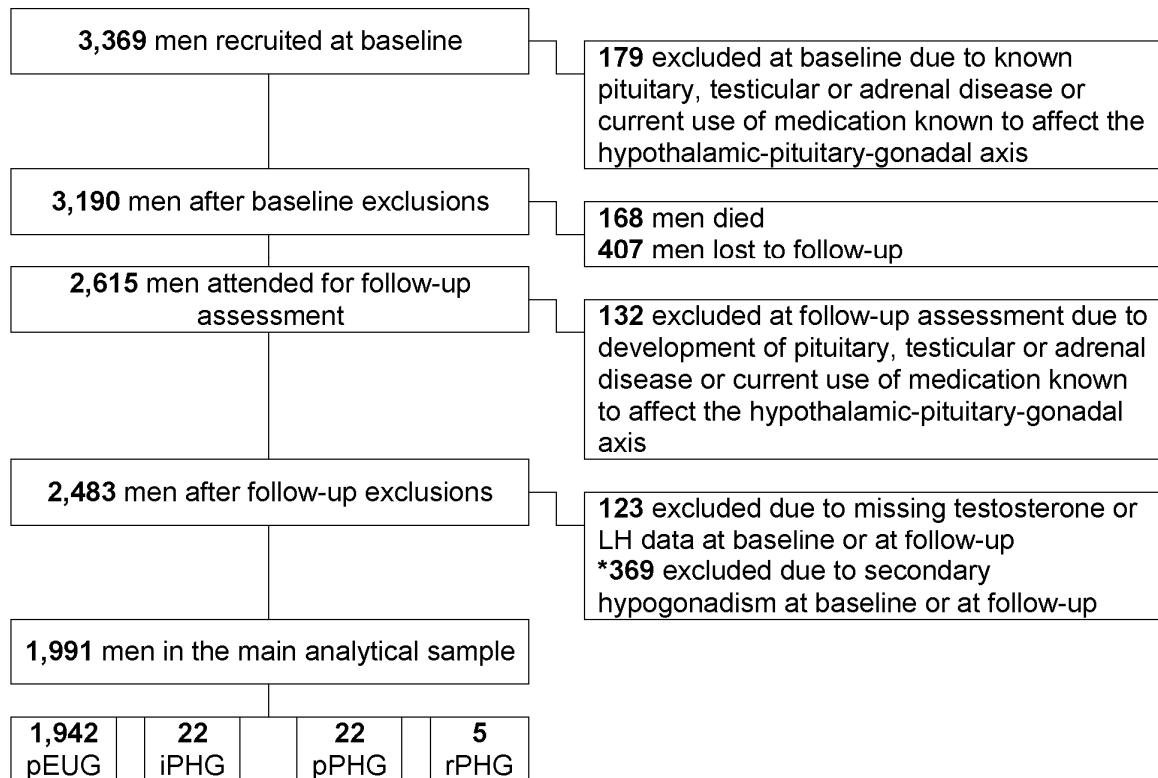
1. P values were calculated using baseline parameters and either Kruskal-Wallis analyses for continuous variables or the Chi squared test for categorical variables.

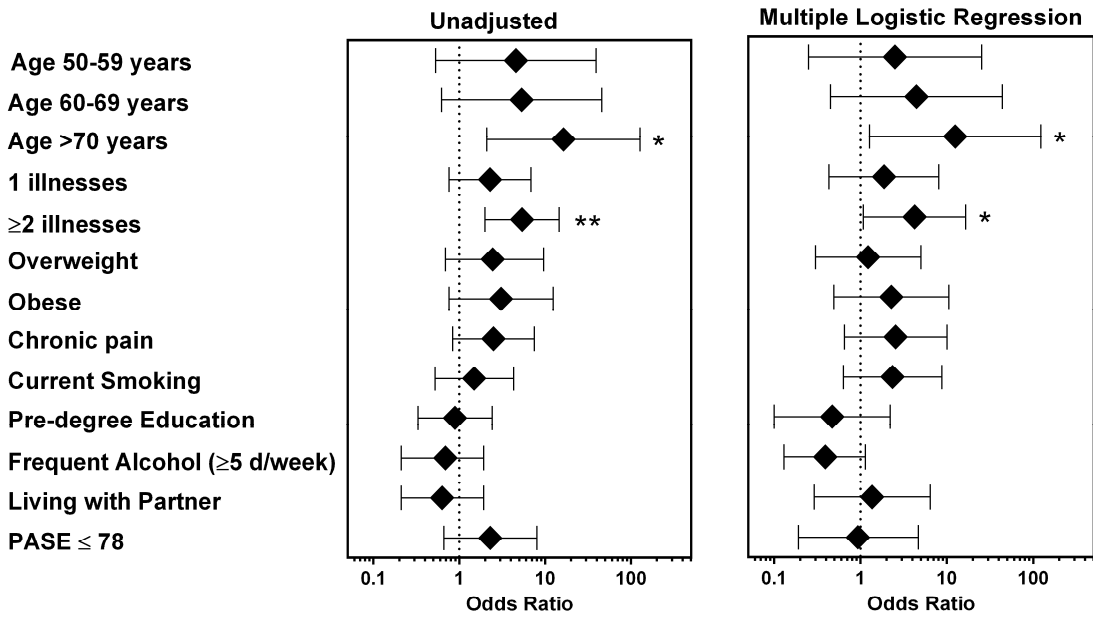
2. P values were calculated using follow-up parameters and either Kruskal-Wallis analyses for continuous variables or the Chi squared test for categorical variables.

^a Data differ significantly ($p < 0.05$) from those in the pEUG group on post-hoc analysis using Tukey-Kramer for continuous variables or the z-test for categorical variables with correction for multiple pairwise comparisons.

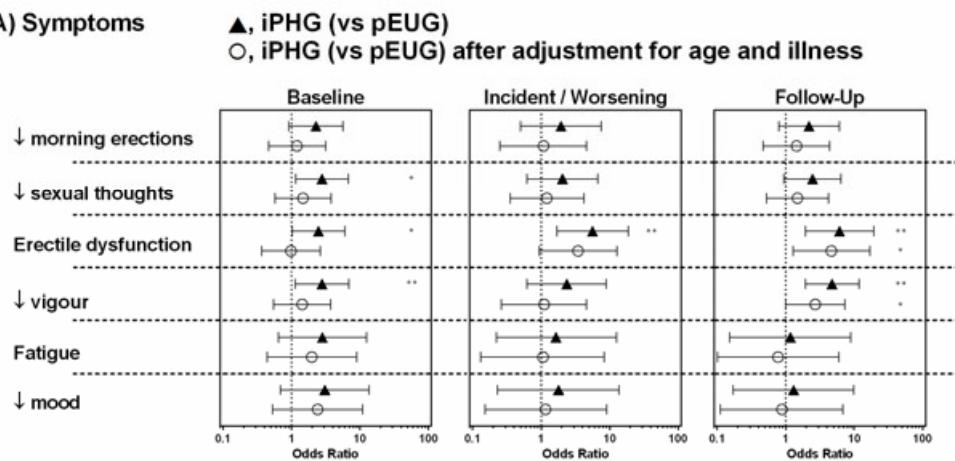
^b Data differ significantly ($p < 0.05$) from those in the iPHG group on post-hoc analysis using Tukey-Kramer for continuous variables or the z-test for categorical variables with correction for multiple pairwise comparisons.

ⁱ Data differ from baseline values within the same group when analysed using Wilcoxon Signed Ranks Test or the McNemar test.

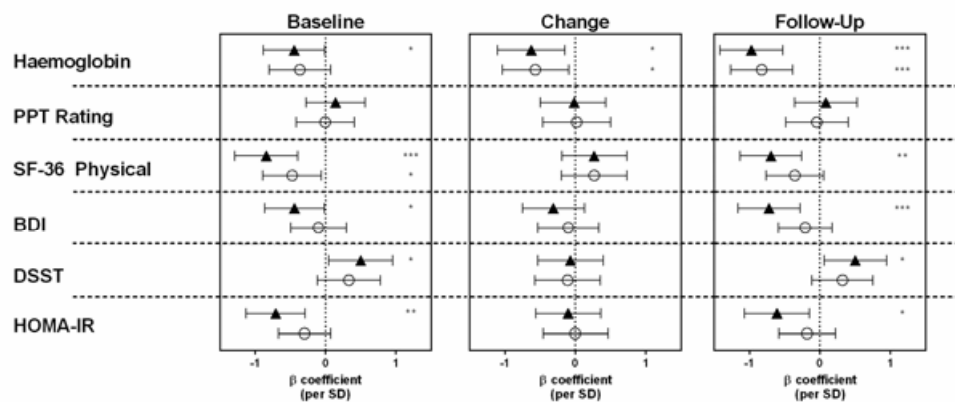




A) Symptoms



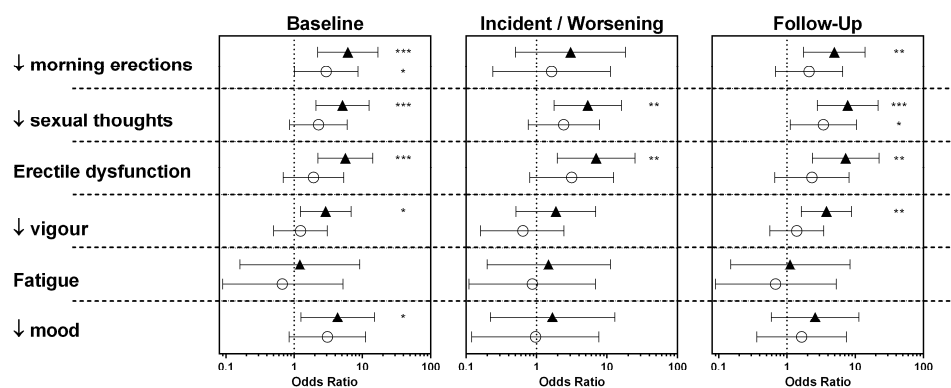
B) Functional Ratings



A) Symptoms

▲, pPHG (vs pEUG)

○, pPHG (vs pEUG) after adjustment for age and illness



B) Functional Ratings

